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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BOWMAN, AMY HUDSON	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/720,448	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 November 2003 and 19 May 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/9/07, 10/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant has cancelled claims 1-51 and added new claims 52-56.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 7/9/07 and 10/4/07 have been considered by the examiner.

;

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. None of the prior-filed applications teach the following limitations: a siRNA molecule having a sense and an

antisense strand of any length wherein the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-flouro modifications and the antisense strand comprises 10 or more 2'-O-methyl and 2'-deoxy-2'-flouro modifications. The priority documents do not each teach these elements in combination with the structural elements of claims 53-56.

Furthermore, the claims read on any siRNA wherein the sense strand is at least 10 nucleotides in length and the antisense strand is at least 20 nucleotides in length (10 or more 2'-O-methyl **and** 2'-deoxy-2'-flouro nucleotides), as long as the instant modifications are present, which is not supported by the priority documents.

Therefore, the instant claims are accorded an effective filing date of 11/24/03, the filing date of the instant application.

Upon a review of the priority documents, support for the limitations set forth above is not evident in the context of the instant claims. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation in each of the claimed priority documents specifically in the combined context as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The instant specification does not disclose a siRNA molecule having a sense and an antisense strand of any length wherein the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-flouro modifications and the antisense strand comprises 10 or more 2'-O-methyl and 2'-deoxy-2'-flouro modifications. The specification also does not each teach these elements in combination with the structural elements of claims 53-56.

Furthermore, the claims read on any siRNA wherein the sense strand is at least 10 nucleotides in length and the antisense strand is at least 20 nucleotides in length (10 or more 2'-O-methyl **and** 2'-deoxy-2'-flouro nucleotides), as long as the instant modifications are present, which is not supported by the instant specification.

MPEP §2163.06 notes:

> If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

> Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at

the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

A review of the specification does not reveal support for where the claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 5/19/09.

There is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 11/24/03, which is the filing date of the instant application.

Claims 52-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific examples of active molecules that fall within the instant genus in the specification, does not reasonably provide enablement for any nucleic acid molecule within the instant genus being active. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The instant invention is drawn to any siRNA molecule directed to any target wherein the siRNA molecule is of any length, as long as the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-flouro modifications and the antisense strand comprises 10 or more 2'-O-methyl and 2'-deoxy-2'-flouro modifications.

Therefore, the claims read on any siRNA wherein the sense strand is at least 10 nucleotides in length and the antisense strand is at least 20 nucleotides in length (10 or more 2'-O-methyl **and** 2'-deoxy-2'-flouro nucleotides) with the instant modifications with a resultant activity of acting via RNAi, the only utility of the instant molecules in the instant specification.

When considering the huge possible genus of molecules with every possible combination within this genus, the instant specification does not set forth a structural characteristic within this genus to describe which molecules would in fact have the function of targeting and inhibiting target gene expression, which is the only utility of the molecules in the instant specification.

One of skill would not be able to recognize that applicant was in

possession of such a huge genus of molecules that would act via RNAi with such variation in strand lengths with no length limit and no specific stringency with a target sequence and such extensive modification.

One would not be able to readily envision the genus of active molecules within such a large genus being claimed and therefore would not be able to recognize that applicant was in possession of such a genus at the time of filing.

It would require undue experimentation for the skilled artisan to determine which other species would actually be active; as it is known in the art to that extensive modification may result in abolishment of RNAi activity.

The species that have been exemplified in the instant specification are not demonstrative of any siRNA within the instant genus. The specification is enabling for the specific examples set forth in the specification, however are not enabling for the full scope of the instant claims as the claims embrace siRNAs that are modified with a huge genus of possible combinations of modifications at a huge genus of percentages that would require undue experimentation to determine which are active and which are not. The figures of the instant application are evidence that some of the siRNA molecules retain activity while others don't.

Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001) (of record and cited on the PTO-892 mailed on 7/19/07) teaches that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished RNAi activity and is therefore evidence that extensive modification yields unpredictable results with siRNA molecules. This coupled with the lack of

exemplification to support such a broad genus as instantly claimed results in the need for undue experimentation to determine which species within the instant genus would in fact be active.

There is no guidance in the specification as filed that teaches that the instant genus would be expected to be active or that teaches a structural requirement to narrow the instant genus to those that would be active.

As outlined above, it is well known that there is a high level of unpredictability in the RNAi art for extensively modifying siNA molecules that remain active. Furthermore, the claims have very loose length requirements and no stringency requirements with regards to a target sequence. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely in determining which species within the instant huge genus would in fact have the instant utility of silencing target gene expression.

MPEP 2164.01
Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.

Also, MPEP 2164.01(a)
A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* which species of molecules within the instant huge genus would in fact have RNAi activity. Without further guidance, one of

skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the **full scope** of the claimed invention without undue experimentation (see MPEP 2164.01(a)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 52-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Nyce (WO 99/13886), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Matulic-Adamic et al. (US 5,998,203), Bertrand et al. (Biochemical and Biophysical Research Communications, 2002, 296, pages 1000-1004), Braasch et al. (Biochemistry, 2002, Vol. 41, No. 14, pages 4503-4510), and Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109).

The instant claims are directed to a siRNA molecule having a sense and an antisense strand wherein the sense strand comprises 10 or more 2'-deoxy, 2'O-methyl, or 2'-deoxy-2'-flouro nucleotides and the antisense strand comprises ten or more 2'-O-methyl **and** 2'-deoxy-2'-flouro nucleotides. The claims are further directed to 10 or more pyrimidines of the sense strand, antisense strand, or both being 2'-deoxy, 2'O-methyl, or 2'-deoxy-2'-flouro; the sense and/or antisense strand comprises phosphorothioates, and to a composition comprising the siRNA molecule and a pharmaceutically acceptable carrier.

The instant rejection is applied against siRNA molecules within the instant genus that are enabled. The instant rejection is based upon the obviousness to modify within the instant genus of modifications wherein pyrimidines are modified with the modifications of claim 53, although the entire genus is not enabled as set forth in the rejection under 35 USC 112, 1st paragraph above.

Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. The siRNAs taught by Elbashir et al. mediated RNAi via RISC. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications that retained activity.

Elbashir et al. teaches that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function (see page 6886, column 2); modifying terminal nucleotides (see page 6881), meeting the instant limitation

of a terminal cap; the siRNA molecules comprise ribonucleotides (see Fig. 1, for example); duplexes of 21 nt siRNAs with 2 nt 3'-overhangs were the most efficient triggers of sequence-specific mRNA degradation (see abstract, for example); modification of the overhangs (see page 6881); wherein the siRNA is in a composition with a pharmaceutically acceptable diluent, such as buffer (see Materials and methods, page 6886).

Elbashir et al. do not teach double stranded nucleic acid molecules with combinations of modifications at the instant number of positions and do not teach phosphorothioates.

Elbashir et al. do not teach 2'-deoxy-2'-flouro modifications, although the claims do not require such, as this is just one species of the genus.

Nyce teaches antisense oligonucleotides that attenuate the expression of target mRNA. The oligonucleotides are preferably up to about 30 nucleotides in length, more preferably up to about 21 nucleotides in length (see page 16). Nyce teaches antisense oligonucleotides targeted specifically to human muscarinic acetylcholine receptor 3 (CHRM3) (see page 54). Nyce teaches phosphorothioate, 2'-deoxy and 2'-O-methyl modification of the oligonucleotides at various percentages of the purine and/or pyrimidine residues, including 100% substitution (see page 73) for enhancing the uptake of the oligonucleotides. The 100% substituted oligonucleotide comprises a phosphorothioate at the 3' end. Nyce teaches compositions comprising the oligonucleotide and a pharmaceutically acceptable carrier (see page 77). Nyce teaches surfactants or

surfactant components bound to the 5' and/or 3' ends or the oligonucleotides for enhancing uptake of the oligonucleotide (see page 80).

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with complete modification with 2'-fluorouracil modifications. However, it

is noted that the instant claims do not recite any upper length limitation. Furthermore, the extensively modified dsRNA of Parrish et al. resulted in strong RNAi activity.

Bertrand et al. teach a comparison of antisense oligonucleotides and siRNAs. Bertrand et al. teach that siRNAs appear to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides. Bertrand et al. teach that siRNA activity, but no antisense oligonucleotide activity, was observed in mice, probably due to the lower resistance to nuclease degradation of antisense oligonucleotides (see abstract). Bertrand et al. teach that siRNAs are composed of small double-stranded RNA oligonucleotides with a length of 21/22 bases (see page 1000, column 1). Bertrand et al. teach that delivery is a very similar issue for both approaches and that siRNAs are very promising tools for gene inhibition *in vivo* (see page 1000, column 2).

Braasch et al. teach that the need for antisense oligomers that are more potent and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity (see page 4503). Braasch et al. teach goals for improving oligonucleotides including: improve pharmacokinetics, tissue distribution, and targeting; characterize the mechanism of RNA interference and its full potential for inhibition of gene expression for cell culture studies; use RNAi for in vivo inhibition of mammalian gene expression; perform comparative studies to demonstrate the relative strengths of different oligomer chemistries for given applications (i.e. morpholino versus RNAi) (see Table 2). Braasch et al. teach that if good *in vivo* uptake can

be achieved, RNAi might significantly improve the ability of oligonucleotides to have an impact (see page 4509).

Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. added chemical modifications to ribonucleotides at either of the two ends of an oligonucleotide sequence, or the center region together with different combinations of phosphodiester/phosphorothioate backbones and investigated the effect on the activity of antisense oligonucleotides. The gapmer oligonucleotide exhibited a potent bispecific antisense activity. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides.

It would have been obvious to synthesize a siRNA with the structural characteristics taught by Elbashir et al. with modifications within the instant genus and wherein 10 or more pyrimidines are modified with the instant modifications.

Furthermore, it would have been obvious to incorporate each of the instant types of chemical modifications or combinations of chemical modifications, as each of the types of modifications are taught by Elbashir et al., Matulic-Adamic et al., or Parrish et al. to enhance nucleic acid inhibitory molecules.

It would have been obvious to incorporate the modifications differentially between purines or pyrimidines because the genus of possible places to incorporate the known modifications is very small (pyrimidine or purine). When incorporating modifications in nucleic acids, the modifications are incorporated into a purine or a pyrimidine. Given that the modifications were known in the art to benefit nucleic acid stability, and it was known to incorporate the same modifications from antisense/ribozyme technology into siRNAs, wherein the only possible places to incorporate the modifications is on a purine or a pyrimidine, it would have been obvious to incorporate the instant modifications into at least 10 nucleotides of the sense strand or twenty nucleotides of the antisense strand in combination with the specific modification of 10 or more pyrimidines and this is considered within the realm of routine optimization.

One would have been motivated to synthesize a siRNA molecule, as taught by Elbashir et al., Nyce teaches antisense oligonucleotides and teaches modifications thereof (phosphorothioate, 2'-deoxy and 2'-O-methyl modification of the oligonucleotides at various percentages of the purine and/or pyrimidine residues, including 100% substitution (see page 73)) for enhancing the uptake of the oligonucleotides. Therefore, one would have been motivated to incorporate the same types of modifications into a siRNA for the same purpose of enhancing uptake of the molecule, especially given that Bertrand et al. teach a comparison of antisense oligonucleotides and siRNAs and teach that siRNAs appear to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides. Furthermore, Bertrand et al. teach that siRNA technology can

be applied in the same delivery situations that have been previously studied with antisense oligonucleotides.

One would have been motivated to incorporate 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al. or Matulic-Adamic et al., as well as 2'-O methyl, 2'-deoxy modifications, and phosphorothioates, as taught by Matulic-Adamic et al., as each of these chemical modifications, as well as various combinations of chemical modifications, were known in the art to protect nucleic acids from exonuclease degradation and enhance the activity of nucleic acids, as taught by Matulic-Adamic et al. One would have been motivated to incorporate the modifications on purines or pyrimidines as a matter of optimization of the activity of the siRNA, given there are only two choices.

As explained in the rejection under 35 USC 112 above, the instant genus is huge. It is considered that there would be some configuration of the chemical modifications that were known in the art to benefit other nucleic acid molecules such as antisense oligonucleotides or ribozymes that would retain RNAi activity when incorporated into nucleic acid molecules. Due to the breadth of the instant claims, the teachings of Elbashir et al. are considered to be motivation with regards to extensively modifying nucleic acid duplexes to optimize the activity therein. Although Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity, there are no instant claims that are identical in scope to the teachings of Elbashir et al. Therefore, within the huge genus of molecules that are being instantly claimed, the teachings of Elbashir et al. are considered to offer motivation to test various

types of known chemical modifications at different percentages in order to optimize the activity of the molecule.

It is noted that ribozymes are sequence specific inhibitory nucleic acid molecules that rely on activity with a complex secondary structure. Although ribozymes are faced with the complexity of structure, it is well known in the nucleic acid art to incorporate extensive levels of chemical modification to enhance the activity of the molecule and to specifically incorporate each of the instantly recited modifications, as evidenced by Matulic-Adamic et al.

The instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see pages 109-110).

It is acknowledged that the specification is not to be relied upon for a source of motivation and that is not considered to be the instant case. The specification is merely being relied upon to distinguish that applicant recognized that double stranded nucleic acid modification is dependent upon the state of the art of oligonucleotides and ribozymes and that previously beneficial chemical modifications would be used with double stranded nucleic acid molecules as well.

Furthermore, Braasch et al. teach that the need for antisense oligomers that are more potent and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity. Braasch et al. further recognize that goals to improve RNAi can be accomplished by utilizing chemical modifications. Since Braasch et al. teach that chemical modifications yield more potent and more selective antisense oligomers, such as oligomers for RNAi, and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression, the gene expression of Elbashir et al. and Parrish et al. being inhibited by RNAi, one would have been motivated to synthesize duplexes with different levels of modifications to optimize the activity of the molecule.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters the same problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the same benefits to RNAi technology.

For example, Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. teach that combinations of different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Olie et al. teach stepwise experimentation of

modifications throughout oligonucleotides in order to find the optimal configuration. Olie et al. is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations and amounts, as taught by Olie et al., into the siRNA duplexes that were synthesized by Elbashir et al.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes, as evidenced by Elbashir et al., Nyce, Matulic-Adamic et al., Parrish et al. and Olie et al., wherein each of the molecules face similar delivery challenges, and each of which can be improved with modifications, as evidenced by Braasch et al. Since Olie et al. teach effectively walking modifications across antisense oligonucleotides to optimize the combination of modifications as well as the location of the modifications and Elbashir et al. and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for modifications at various percentages to benefit the double stranded nucleic acid molecules of Elbashir et al.

Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach extensive modification of double stranded nucleic acid molecules and Olie et al. teach experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating the modifications at various

percentages in the double stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 8-21 of copending Application No. 11/502,876 and claims 1, 2, 5-9, 11, 13, 14, and 17-31 of application 11/502,893 Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are directed to double stranded nucleic acid molecules with substantially similar and overlapping structural characteristics, wherein the claims of the conflicting applications do not recite a specific target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/170,290. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with

overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '290 are specific for a BACE gene, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/185,652. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '652 are specific for a human c-Fos RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/204,572. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the

claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '572 are specific for a human ECGF1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/203,055. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '055 are specific for a human VCAM-1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/200,736. Although the conflicting claims are not

identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '736 are specific for a Cyclin D1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/203,731. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '731 are specific for a human CHRM3 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of

copending Application No. 12/204,612. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '612 are specific for a human MMP13 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/175,367. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '367 are specific for a human HIF1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 129-138 of copending Application No. 10/444,853. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are directed to double stranded nucleic acid molecules with substantially similar and overlapping structural characteristics, wherein the instant claims do not recite a target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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